General

Guideline Title

Management of early-stage Hodgkin lymphoma.

Bibliographic Source(s)

Herst J, Crump M, Baldassarre F, MacEachern J, Sussman J, Hodgson D, Cheung M, Hematology Disease Site Group. Management of early-stage Hodgkin lymphoma. Toronto (ON): Cancer Care Ontario (CCO); 2015 Dec 8. 126 p. (Program in Evidence-based Care Guideline; no. 6-20). [66 references]

Guideline Status

This is the current release of the guideline.

The Program in Evidence-based Care guideline, initially the full original Guideline, over time will expand to contain new information emerging from their reviewing and updating activities.

Please visit the Cancer Care Ontario (CCO) Web site for details on any new evidence that has emerged and implications to the guidelines.

This guideline meets NGC's 2013 (revised) inclusion criteria.

Recommendations

Major Recommendations

Recommendation 1A

Patients with early-stage classical Hodgkin lymphoma (HL) should not be treated with radiotherapy alone.

Recommendation 1B

In patients with early-stage nodular lymphocyte predominant HL (NLPHL), it is reasonable to use involved-field radiation therapy alone. However, no phase III clinical trials have focused exclusively on NLPHL, therefore, no strong evidence base for such treatment, or for relative dosage, is currently available, and this recommendation is based on the expert opinion of the guideline authors.

Recommendation 2

Chemotherapy plus radiotherapy or chemotherapy alone are recommended treatment options for patients with early-stage nonbulky HL.

Recommendation 3

When delivered as part of a planned combined modality treatment approach, involved field radiation therapy (IFRT) should be used for patients with early stage HL.

Recommendation 4

The dose of involved field radiation should be 20 Gy for patients with favourable characteristics and between 30 to 36 Gy for patients with unfavourable characteristics (see Appendix 1 in the original guideline document for definitions of favourable and unfavourable characteristics).

Recommendation 5

The Working Group does not recommend the use of a negative interim positron emission tomography (PET) scan alone to identify patients with early-stage HL for whom radiotherapy can be omitted without a reduction in progression free survival (PFS).

Recommendation 6A

Patients with early-stage, favourable risk HL who are being treated with combined modality therapy should receive two cycles of chemotherapy before radiotherapy.

Recommendation 6B

Patients with early-stage, unfavourable risk HL, who are being treated with combined modality therapy, should receive four cycles of chemotherapy before radiotherapy.

Recommendation 7

Doxorubicin, bleomycin, vinblastine, and dacarbazine (ABVD) should be the regimen of choice when administered before radiotherapy, except under the circumstances that follow in Recommendation 8.

Recommendation 8

Patients with early-stage, unfavourable risk HL may be considered for treatment with either four cycles of ABVD, or two cycles of escalated bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine and prednisone (BEACOPP) followed by two cycles of ABVD before radiotherapy.

Clinical Algorithm(s)

None provided

Scope

Disease/Condition(s)

Early-stage Hodgkin lymphoma (HL)

Guideline Category

Management

Treatment

Clinical Specialty

Hematology

Oncology

Radiation Oncology

Intended Users

Advanced Practice Nurses

Nurses

Physician Assistants

Physicians

Guideline Objective(s)

To make recommendations on management strategies for patients with early-stage Hodgkin lymphoma (HL)

Target Population

Patients with early-stage Hodgkin lymphoma (HL)

Interventions and Practices Considered

1. Chemotherapy alone
    - Doxorubicin, bleomycin, vinblastine, and dacarbazine (ABVD)
    - Bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine and prednisone (BEACOPP)
2. Involved field radiation therapy (IFRT) (20 Gy for patients with favourable characteristics or 30-36 Gy for patients with unfavourable characteristics)
3. Chemotherapy prior to radiotherapy

Note: The following interventions were considered but not recommended:

- Radiotherapy alone
- Negative interim positron emission tomography scan alone

Major Outcomes Considered

- Overall survival (OS) rate
- Event-free survival (EFS) and progression-free survival (PFS)
- Freedom-from-treatment-failure (FFTF) rate
- Response
- Quality of life
- Recurrence rate
- Adverse events (early and late)

Methodology

Methods Used to Collect/Select the Evidence

Hand-searches of Published Literature (Primary Sources)

Hand-searches of Published Literature (Secondary Sources)

Searches of Electronic Databases

Description of Methods Used to Collect/Select the Evidence

Search for Existing Guidelines

A search for existing guidelines is generally undertaken prior to searching for existing systematic reviews or primary literature. This is done with the goal of identifying existing guidelines for adaptation or endorsement in order to avoid the duplication of guideline development efforts across jurisdictions.

A search for existing guidelines for possible adaptation or endorsement was conducted jointly to the search for systematic reviews (see Appendix 3 in the original guideline document for search strategies).

One guideline was included, however, the Working Group decided that it could not be endorsed because an Ontario focused evidence-based document was needed. This guideline was used as the evidence-base for one of the recommendations.

Search for Existing Systematic Reviews

A search was conducted for existing systematic reviews. Identified systematic reviews were evaluated based on their clinical content and relevance.

Literature Search Strategy

The literature was systematically searched using the electronic databases MEDLINE (Ovid, 2003 to June 19, 2015), EMBASE (Ovid, 2003 to 2015 Week 25), and the Cochrane Library (Central Register of Controlled Trials, Database of Systematic Reviews, and Database of Abstracts of Effects, 2003 to June 19, 2015). Appendix 3 of the original guideline shows the search strategies used for the MEDLINE and EMBASE databases. This search was adapted for the other databases.

In addition, abstracts from the American Society of Hematology (ASH) (2003 to 2015), the American Society of Clinical Oncology (ASCO) (2003 to 2015), the Lugano International Conference on Malignant Lymphoma, and the Cologne International Symposium on Hodgkin Lymphoma (2003 to 2012) were searched. Working Group members' files and reference lists of included articles were also searched. The database Clinicaltrials.gov was searched for ongoing trials.

Study Selection Criteria and Process

Studies were selected for inclusion in this systematic review if they were:

- Studies of patients treated for early-stage Hodgkin lymphoma (HL) who were of age >15 years
- Studies of systemic treatment for early-stage HL, including chemotherapy, biological agents, field and dose of radiation therapy (e.g., involved field or involved nodes radiotherapy [IFRT or INRT]), or a combination of the above
- Study designs including systematic reviews (SR) published from 2011 to current, and randomized controlled trials (RCTs) published from 2003 to current
- Studies that reported on the following outcomes:
    - Overall survival (OS)
    - Disease control (e.g., progression free survival [PFS])
    - Response
    - Quality of life
    - Adverse events (early and late)
- Published in English

Studies were excluded if they were:

- Systematic reviews published in abstract format only
- Studies including patients receiving treatment for advanced stage HL
- Studies including early and advanced stage HL, and with no separate data for the early-stage population
- Abstract publication of interim analyses (although these will be discussed in the section on ongoing trials in the original guideline document)
- Narrative reviews
- Non randomized trials
- Studies of positron emission tomography (PET) used for staging
- RCTs with sample size <30 patients
- Studies including age groups other than 15 years and over, and with no separate results for the age group of interest

The methodologist and three of the clinicians from the Working Group reviewed independently, in duplicate, the titles and abstracts identified by the search. For those items that warranted full text review, four reviewers in teams of two reviewed each item independently. Discrepancies were resolved by consensus.

General Search Results

The search of electronic databases, conference abstracts, the files of the Working Group members, and the reference lists of included articles resulted in 2233 citations after deduplication, of which 778 came from MEDLINE, 463 from EMBASE, 61 from the Cochrane Library, and 926 from other sources.

The full text of 136 articles was retrieved and independently reviewed by two authors. The full text of one publication could not be located. Eighty-nine articles were excluded: 21 were duplicate publications, six were abstracts of interim analyses, eight did not report on any outcomes of interest, 25 did not report on the population of interest, one did not report on any interventions of interest, 22 did not have the design of interest, six were systematic reviews with a search strategy older than two years or were abstract reports of systematic reviews. Three articles were used only as background information. Forty-four publications were included in this review. Appendix 4 of the original guideline shows the study flow chart.

Among 44 included publications were: one guideline, two systematic reviews of summary data, two meta-analyses of individual-patient data, one in abstract form, and one fully published; seven pooled analyses/subgroup analyses or long-term follow-up of published RCTs reported in nine publications and 32 publications of RCTs.

The members of the Working Group decided not to use any of the systematic reviews captured by the searches as an evidentiary base, or to endorse any of the existing guidelines, because the differences in questions, definitions of the early-stage HL population or provincial context were enough to make their content unfit as a base for this Ontario-based guideline. The systematic reviews retrieved were used as a source of evidence.

Number of Source Documents

- Radiotherapy Question: 17 randomized controlled trials (RCTs), represented by 21 publications were included.
- Chemotherapy Question: 9 studies, represented by 11 publications were included. In addition, three studies that had been identified for the radiotherapy question also addressed a chemotherapy question.

See Appendix 4 in original guideline document for a flow diagram depicting the study selection process.

Methods Used to Assess the Quality and Strength of the Evidence

Expert Consensus

Rating Scheme for the Strength of the Evidence

Not applicable

Methods Used to Analyze the Evidence

Meta-Analysis

Review of Published Meta-Analyses

Systematic Review with Evidence Tables

Description of the Methods Used to Analyze the Evidence

Data Extraction and Assessment of Study Quality and Potential for Bias

The methodologist extracted data from the studies included after full text review and completed evidence tables. One of the clinicians in the working group reviewed for correctness the tables of general characteristics, results, and adverse events.

The quality of the included studies was evaluated according to the Cochrane Risk of Bias tool independently by the methodologist and by one of the clinicians in the Working Group. The GRADEprofiler (GRADEpro) tool was used to create the evidence profile and summary-of-findings tables considering the quality of the evidence for each outcome. Discrepancies were resolved by consensus.

The members of the Working Group identified nine relevant comparisons that were used to extract the data and synthesize the evidence:

Radiotherapy Question

A. Chemotherapy alone versus chemotherapy + radiotherapy
B. Low radiotherapy dose versus high radiotherapy dose
C. Small radiotherapy field versus large radiotherapy field
D. Small radiotherapy field plus chemotherapy versus large radiotherapy field alone
E. Standard therapy versus tailored therapy using fluorodeoxyglucose positron emission tomography (FDG-PET) scanning

Chemotherapy Question

F. Chemotherapy plus radiotherapy versus radiotherapy alone
G. Less intensive chemotherapy regimens plus radiotherapy versus more intensive regimens plus radiotherapy
H. More intense chemotherapy plus radiotherapy versus less intensive regimens plus radiotherapy
I. More cycles of a specific chemotherapy plus radiotherapy versus fewer cycles of the same chemotherapy plus radiotherapy

Synthesizing the Evidence

When clinically homogeneous results from two or more trials were available, a meta-analysis was conducted using the Review Manager software (RevMan 5.2) provided by the Cochrane Collaboration. For time-to-event outcomes, hazard ratios (HR), rather than the number of events at a certain time point, are the preferred statistic for meta-analysis, and are used as reported. If the HR and/or its standard error were not reported, they have been derived from other information reported in the study, if possible, using the methods described by Parmar et al. For all outcomes, the generic inverse variance model with random effects, or other appropriate random effects models in Review Manager have been used.

Statistical heterogeneity was calculated using the χ^2 test for heterogeneity and the I^2 percentage. A probability level for the χ^2 statistic less than or equal to 10% ($p \leq 0.10$) and/or an I^2 greater than 50% was considered indicative of statistical heterogeneity.

If data was not considered sufficiently clinically and statistically homogeneous, a narrative synthesis was performed.

Methods Used to Formulate the Recommendations

Expert Consensus

Description of Methods Used to Formulate the Recommendations

Guideline Developers

This guideline was undertaken by the Early-Stage Hodgkin Lymphoma guideline development group (see Appendix 2 in the original guideline document), which was convened at the request of the Hematology Disease Site Group. The project was led by a small Working Group of the Early-Stage Hodgkin Lymphoma guideline development group which was responsible for reviewing the evidence base, drafting the guideline recommendations and responding to comments received during the document review process. The members of the Working Group had expertise in hematology, radiation oncology and health research methodology. Other members of the Disease Site Group served as the Expert Panel and were responsible for the review and approval of the draft document produced by the Working Group.

Guideline Development Methods

The Program in Evidence-based Care (PEBC) produces evidence-based and evidence-informed guidance documents using the methods of the Practice Guidelines Development Cycle. This process includes a systematic review, interpretation of the evidence by the members of the Working Group and draft recommendations, internal review by content and methodology experts and external review by Ontario clinicians and other stakeholders.

The PEBC uses the Appraisal of Guidelines, Research and Evaluation II (AGREE II) framework as a methodological strategy for guideline

development. AGREE II is a 23-item validated tool that is designed to assess the methodological rigour and transparency of guideline development.

PEBC guideline development methods are described in more detail in the PEBC Handbook and the PEBC Methods Handbook (see the "Availability of Companion Documents" field).

Research Questions

1. What are the optimum radiation dose and schedule and what are the best chemotherapy regimens for the treatment of patients with early-stage Hodgkin lymphoma (HL)?
2. What are the best strategies for the prevention of early and late adverse events in patients with early-stage HL?
3. What is the role of positron emission tomography (PET) in guiding therapeutic decisions in the management of early-stage HL?
4. What are the best strategies for the treatment of subgroups of patients with early-stage HL, such as those with very favourable or unfavourable disease?

Methods

This evidence review was developed using a planned two-stage method. The members of the Working Group decided to answer the questions in two parts: the initial questions were answered considering first radiotherapy, and then chemotherapy treatment.

Rating Scheme for the Strength of the Recommendations

Not applicable

Cost Analysis

A formal cost analysis was not performed and published cost analyses were not reviewed.

Method of Guideline Validation

External Peer Review

Internal Peer Review

Description of Method of Guideline Validation

Guideline Review and Approval

Internal Review

For the guideline document to be approved, 75% of the content experts who comprise the Guideline Development Groups (GDG) Expert Panel must cast a vote indicating whether or not they approve the document, or abstain from voting for a specified reason, and of those that vote, 75% must approve the document. In addition, the Program in Evidence-based Care (PEBC) Report Approval Panel (RAP), a three-person panel with methodology expertise, must unanimously approve the document. The Expert Panel and RAP members may specify that approval is conditional, and that changes to the document are required. If substantial changes are subsequently made to the recommendations during external review, then the revised draft must be resubmitted for approval by RAP and the GDG Expert Panel.

External Review

Feedback on the approved draft guideline is obtained from content experts and the target users through two processes. Through the Targeted Peer Review, several individuals with content expertise are identified by the GDG and asked to review and provide feedback on the guideline document. Through Professional Consultation, relevant care providers and other potential users of the guideline are contacted and asked to provide feedback on the guideline recommendations through a brief online survey. This consultation is intended to facilitate the dissemination of the final guidance report to Ontario practitioners.

See Section 5 in the original guideline document for further discussion of the internal and external guideline review process and results.

Evidence Supporting the Recommendations

Type of Evidence Supporting the Recommendations

The recommendations are supported by randomized controlled trials and meta-analyses.

Benefits/Harms of Implementing the Guideline Recommendations

Potential Benefits

Appropriate management of early disease leading to improved survival, disease control, decreased adverse effects of treatment, and quality of life

Potential Harms

Early and late adverse effects of radiotherapy and chemotherapy; including nausea, pharyngeal toxicity, leukopenia, thrombocytopenia, and gastrointestinal adverse effects

Qualifying Statements

Qualifying Statements

- Care has been taken in the preparation of the information contained in this report. Nonetheless, any person seeking to apply or consult the report is expected to use independent medical judgment in the context of individual clinical circumstances or seek out the supervision of a qualified clinician. Cancer Care Ontario (CCO) makes no representation or guarantees of any kind whatsoever regarding the report content or use or application and disclaims any responsibility for its application or use in any way.
- See the original guideline document for qualifying statements related to each specific recommendation.

Implementation of the Guideline

Description of Implementation Strategy

Implementation Considerations

Feasibility

The chemotherapies discussed in the recommendations are currently funded in Ontario. Access to systemic therapies and radiation (involved-field) is well-established in the province and the costs of such care are reasonable. Access to newer technologies, including positron emission tomography (PET) scans and involved nodal radiation, may still be evolving; however, these are not currently an integral component of the recommended care.

Patient Considerations

Outcomes of interest include survival, consideration of balance between upfront disease control and long-term adverse effects, and quality of life. In particular, the recommendations include statements focused on patient-centred decisions.

Equity

The Working Group does not anticipate that the recommendations would increase inequities in care. A Cancer Care Ontario (CCO) priority is to maintain universal (including geographic) access to cancer care.

Provider Considerations

The Working Group hopes the opinions expressed reflect the views of the broad community of clinicians. This guideline is subject to external review.

System Considerations

The recommendations should not impact the current system of care.

Implementation Tools

Quick Reference Guides/Physician Guides

For information about availability, see the *Availability of Companion Documents* and *Patient Resources* fields below.

Institute of Medicine (IOM) National Healthcare Quality Report Categories

IOM Care Need

Getting Better

Living with Illness

IOM Domain

Effectiveness

Patient-centeredness

Identifying Information and Availability

Bibliographic Source(s)

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Adaptation

Not applicable: The guideline was not adapted from another source.

Date Released

2015 Dec 8

Guideline Developer(s)

Program in Evidence-based Care - State/Local Government Agency [Non-U.S.]

Guideline Developer Comment

The Program in Evidence-based Care (PEBC) is a Province of Ontario initiative sponsored by Cancer Care Ontario (CCO) and the Ontario Ministry of Health and Long-Term Care.

Source(s) of Funding

The Program in Evidence-based Care (PEBC) is a provincial initiative of Cancer Care Ontario (CCO) supported by the Ontario Ministry of Health and Long-Term Care (OMHLTC). All work produced by the PEBC is editorially independent from the OMHLTC.

Guideline Committee

Hematology Disease Site Group

Composition of Group That Authored the Guideline

Authors: J. Herst, M. Crump, F. Baldassarre, J. MacEachern, J. Sussman, D. Hodgson, M. Cheung

Financial Disclosures/Conflicts of Interest

In accordance with the Program in Evidence-based Care (PEBC) Conflict of Interest (COI) Policy, the guideline authors, the members of the Hematology Disease Site Group, and internal and external reviewers were asked to disclose potential conflicts of interest. Their responses in this regard are reported in Appendix 2 in the original guideline document. The COI declared in Appendix 2 did not disqualify any individuals from performing their designated role in the development of this guideline, in accordance with the PEBC COI Policy .

Guideline Status

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This guideline meets NGC's 2013 (revised) inclusion criteria.

Guideline Availability

Available from the Cancer Care Ontario (CCO) Web site .

Availability of Companion Documents

The following are available:

- Management of early-stage Hodgkin lymphoma. Summary. Toronto (ON): Cancer Care Ontario (CCO); 2015 Dec 8. 2 p. Available from the Cancer Care Ontario (CCO) Web site .
- Program in Evidence-based Care handbook. Toronto (ON): Cancer Care Ontario (CCO); 2012. 14 p. Available from the CCO Web site .

- Program in Evidence-based Care methods handbook. Toronto (ON): Cancer Care Ontario (CCO); 2014 Sep 23. Available from the Program in Evidence-based Care (PEBC) Toolkit Web site.
- Program in Evidence-based Care document assessment and review protocol. Toronto (ON): Cancer Care Ontario (CCO); 2015 Apr 16. 13 p. Available from the CCO Web site.

Patient Resources

None available

NGC Status

This NGC summary was completed by ECRI Institute on April 4, 2016.

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